REMARKS

Favorable reconsideration of this application, in light of the preceding amendments and following remarks, is respectfully requested.

Claims 1-6, 8-10 and 22 are pending in this application. Claims 1-6 have been withdrawn from consideration. Claims 8 and 10 have been amended. No claims are cancelled or added. Claims 1, 10 and 22 are the independent claims.

Applicants respectfully note that the present action does not indicate that the claim to foreign priority under 35 U.S.C. §119 has been acknowledged or that certified copies of all priority documents have been received by the U.S.P.T.O. Applicants respectfully request that the Examiner's next communication include an indication as to the claim to foreign priority under 35 U.S.C. §119 and an acknowledgement of receipt of the certified copies of all priority documents.

Interview Summary

Applicants wish to thank the Examiner for the courtesies extended during the telephonic interview conducted on December 22, 2009. Applicants submit that the amendment to claim 10 was prepared consistent with the discussion, and thus, is believed to overcome the current rejections as discussed below.

Rejections under 35 U.S.C. § 103

Domard and Granja in view of Baumann and Nettles

Claims 8-10 and 22 stand rejected under 35 U.S.C. § 103(a) as being obvious over WO 2002/078760 (U.S. Publication No. 2004/0171151) to Domard et al. (hereinafter "Domard"), as evidenced by *Industrial Research Ltd Catalog* (Jan. 14, 2009), and *Key Engineering Materials Vols.*, 254, 256 (2004) by Granja et al. (hereinafter "Granja") and in view of *Carbohydrate Res* 1:43-57, (2001) by Baumann et al. (hereinafter "Baumann") and *Tissue Engineering* 8:1009-1016, (2002) by Nettles et al. (hereinafter "Nettles"). Applicants respectfully traverse this rejection for the reasons detailed below.

Applicants note that the Examiner acknowledges that *Domard* does not disclose (A) whether the chitosan is homogenously reacetylated or (B) whether the chitosan has a molecular weight of not smaller than 200 kDa. However, the Examiner asserts that the chitosan and hydrogel taught by *Domard* are substantially similar to those instantly claimed and are produced by a substantially similar process, respectively. Applicants respectfully disagree.

First, Applicants point out to the Examiner that claims 10 and 22 specifically require that the homogeneously reacetylated chitosan is suitable for preparing a pseudo-thermosetting neutralized chitosan composition forming a phosphate-free transparent hydrogel at a temperature higher than 5°C. Thus, the homogeneously reacetylated chitosan must be capable of forming a

phosphate-free transparent hydrogel. However, none of the references cited teach or suggest a homogeneously reacetylated chitosan which is homogeneously reacetylated to an extent sufficient to enable it to form a transparent hydrogel. Accordingly, Applicants submit that the fact that the homogeneously reacetylated chitosan must be suitable for use in the preparation of a neutralized chitosan composition which forms a phosphate-free transparent hydrogel implies specific structural features on the homogenously reacetylated chitosan as recited in claims 10 and 22, which are not present in any reacetylated chitosan taught in the cited references.

Further, Applicants submit that where reacetylation is not carried out under the specific homogeneous reacetylation conditions of claim 10, then any attempts to produce a hydrogel from the reacetylated chitosan results either in no formation of a hydrogel, or at best the formation of turbid hydrogels. See comparative examples 8 and 9 in the specification illustrating that where the reacetylation process is carried out without the initial filtration step, at room temperature rather than at a temperature lower than 5°C, or under low stirring rather than fast stirring, the reacetylated chitosan obtained was not able to form a transparent hydrogel.

Regarding *Domard*, the Examiner states that reacetylated chitosan taught by *Domard* must, by necessity, be homogenously reacetylated since homogenous reacetylation is an essential criterion to the formation of

phosphate-free hydrogels on the basis of an incomplete citation of the instant specification (p 8, lines 16-19 of the patent application as originally filed) and assuming implicitly, without providing any detailed reasoning or basis, that the phosphate-free hydrogel of *Domard* would be transparent and have pseudo thermosetting properties.

As acknowledged by the Examiner, *Domard* is silent as to whether the chitosan is homogenously reacetylated. However, in his or her reasoning, the Examiner fails to make a prima facie case of obviousness showing that *Domard* provides any indication of the chitosan being homogenously reacetylated. In particular, the Examiner fails to note that the instant specification discloses also that "*in order to obtain such homogeneous distribution mode of acetylated and deacetylated monomers, the chitosan used for preparing the pseudo-thermosetting composition forming a hydrogel must be a chitosan derived from a chitosan having a deacetylation degree of 80 - 90 % which has been homogeneously reacetylated to a deacetylation degree of 30 - 60 % in conditions allowing a random distribution of acetylated and deacetylated monomers*" (p 8, lines 20-26 of the patent application as originally filed). Applicants stress that *Domard* teaches purification and later acetylation of a chitosan with an acetylation degree <10% (i.e. of 5.2%, therefore a deacetylation degree > 90 %), which, according to the instant specification, would not lead to a homogeneous distribution mode of acetylated and deacetylated monomers, which is said to be

an essential criterion to the formation of transparent and phosphate-free hydrogels.

Further, the Examiner fails to stress that the instant specification discloses also that "*a temperature of the acetic anhydride solution and/or of the cooled chitosan solution higher than 5°C would not allow a homogeneous reacetylation*" (on p 10, lines 24-25 of the patent application as originally filed) and that *"homogeneous conditions during the addition step e) is an essential feature of this process, and they may be obtained by providing a fast stirring during the addition, for example with a stirring propeller. An inadequate stirring, for example with a magnetic stirrer, does not allow a homogeneous reacetylation of chitosan and therefore, the chitosan obtained would not allow the preparation of a pseudo-thermosetting composition forming a transparent hydrogel".* (p 11, lines 1-8 of the patent application as originally filed) but *Domard* fails to teach such reacetylation conditions.

Therefore, Applicants submit that the Examiner's assessment that the reacetylated chitosan taught by *Domard* must, by necessity, be homogenously reacetylated as is recited in claims 10 and 22 fails not only to be supported but also denies the clear indications provided in *Domard* otherwise.

The Examiner further states that the molecular weight of the chitosan in *Domard* would necessarily be more than 200 kDa based on an incomplete interpretation of an internet citation (Industrial Research Ltd Catalog) which

was not part of the prior art at the time of filing the present patent application or based on *Granja*. Applicants respectfully disagree.

As acknowledged by the Examiner, *Domard* is silent whether the chitosan has a molecular weight of not smaller than 200 kDa. However, in his/her reasoning the Examiner concludes from the disclosure of Industrial Research Ltd Catalog mentioning only that *"the chitosan prepared by deacetylating squid chitin is also expected to have a higher molecular weight than chitosan derived from other sources"* that the chitosan obtained from squid endoskeleton disclosed by *Domard* would necessarily be more than 200 kDa.

Further in his/her reasoning the Examiner concludes from *Granja*, which discloses a squid chitosan having a viscosity average molecular weight of 2'480 kDa that although *Domard* does not explicitly disclose the molecular weight of the homogenously reacetylated chitosan, the homogenously reacetylated chitosan taught would have a molecular weight of not smaller than 200 kDa.

Applicants stress that a wide range of molecular weights are available for chitosans obtained from crab or shrimp shells, ranging from about 5 kDa to 2,000 kDa. The fact that a squid endoskeleton may have a higher molecular weight than chitosan derived from other sources such as from crab or shrimp shells (as per Industrial Research Ltd Catalog) or the fact that *Granja* discloses a squid chitosan of 2,480 kDa, does not imply that any chitosan obtained from

the squid endoskeleton, and in particular the one disclosed in *Domard*, would have a molecular weight higher than 200 kDa. Therefore, Applicants respectfully submit that the Examiner's assessment that the reacetylated chitosan taught by *Domard* would necessarily be more than 200 kDa fails to be supported.

With regard to Baumann, the Examiner states that the teaching of *Bauman* would motivate one of ordinary skill in the art to homogenously reacetylate chitosan in an effort to avoid solubility problems associated with heterogeneous reacetylation of chitosan in view of *Domard*.

Applicants submit that *Bauman* teaches that N-cetylation of chitosan with acetic anhydride in methanol is carried out at room temperature, and without any prior elimination of insoluble particles (see page 45, col. 2, second paragraph). As explained previously, carrying out the reacetylation of chitosan at room temperature and without any prior elimination of insoluble particles does not allow for a homogeneously reacetylated chitosan able to form a transparent hydrogel as recited in claims 10 and 22.

Further, Applicants respectfully submit that the Examiner cannot select one particular aspect or parameter in a prior art reference to support some teaching or motivation of these limitations as recited in claims 10 and 22. In particular, Applicants stress that *Bauman* teaches lowering the molecular weight of a commercially available chitosan of 150 kDa and of its acetylation

degree of 0.28 (e.g. deacetylation degree of 72%) by hydrolysis into a chitosan of 29 kDa and an acetylation degree of 0.14 (e.g. deacetylation degree of 86%) to decrease toxicity and viscosity and unease regioselective reactions (p 44).

Further, Applicants respectfully disagree with the Examiner's assessment that *"Bauman al.* do not criticize, discredit, or otherwise discourage a homogenously reacetylated chitosan having a molecular weight of not smaller than 200 kDa and deacetylation degree of 30-60%". In particular, Applicants point to p 44, right column, as an example of Bauman teaching away from the limitations of claims 10 and 22:

- item 2: *"The molecular weight of 150 kD is to be reduced by acidic hydrolysis to a water soluble 29 kD chitosan, DA 0.14, which has a number of advantages over a high molecular-weight water-soluble chitosan"; and*
- item 3: *"The low-molecular-weight sulfated chitosan derivatives are known to be less toxic than the high-molecular-weight derivatives"*

Therefore, Applicants submit that *Bauman* does not teach a homogeneously reacetylated chitosan having a molecular weight of not smaller than 200 kDa and a deacetylation degree of 30 - 60 % obtained from the reacetylation of a chitosan having a deacetylation degree of 80 - 90 %, but rather deacetylation degrees of the chitosans and the molecular weights which

would not intrinsically lead to homogeneous conditions (see citations of the instant specification regarding this aspect).

Therefore, Applicants respectfully submit that the Examiner's arguments that claims 10 and 22 are obvious in view of the combination of *Domard* and *Bauman* not supported.

Regarding *Granja*, Applicants submit that the Examiner cannot select one particular aspect or parameter in a prior art reference (in this case the molecular weight) to support some teaching of this reference or some indication of a given motivation to the skilled person out of its context within the rest of the disclosure.

In particular, Applicants stress that *Granja* discloses a squid chitosan having a viscosity average molecular weight of 2,480 kDa and a degree of acetylation of 0.30 (e.g. deacetylation degree of 70%). Further, *Granja* discloses the heterogeneous deacetylation of this chitosan into a chitosan having a degree of acetylation of 0.14 (e.g. deacetylation degree of 86%).

Granja does not teach or suggest a homogeneously reacetylated chitosan having a molecular weight of not smaller than 200 kDa and a deacetylation degree of 30 - 60 % obtained from the reacetylation of a chitosan having a deacetylation degree of 80 - 90 % as recited in claims 10 and 22 but rather deacetylation degrees of the chitosans which would not intrinsically lead to homogeneous conditions (see citations of the instant specification regarding

this aspect). Therefore, Applicants respectfully submit that the Examiner's arguments that claims 10 and 22 are rendered obvious in view of the combination of *Domard* and *Granja* is not supported.

Regarding *Nettles*, the Examiner states that the teaching of *Nettles* (relating to the use of chitosan as a porous scaffold for cartilage tissue engineering) would lead the skilled person to "reasonably predict that altering the molecular weight of the chitosan would provide scaffolds useable in the invention taught by *Domard* having the most desirable properties" based on the very general disclosure of *Nettles* saying that *"the properties of porous chitosan matrices such as microstructure, crystallinity and mechanical strength can be varied by altering chitosan concentration, freezing rate, molecular weight and percent of deacetylation of the starting material."*

First, Applicants submit that "the most desirable properties" for a skilled person in the field of the invention from *Domard.* (i.e. cartilaginous neo-tissue comprising contacting a chitosan hydrogel with a culture of chondrocyte cells in order to get adherence between the chitosan hydrogel and cultured chondrocyte cells and to lead to the development of a cartilaginous neo-tissue in contact with the surface of the chitosan hydrogel) and a skilled person in the field of building porous scaffold for cell attachment in cartilage tissue engineering (*Nettles*) are very different. The teachings of *Nettles* are remote

from the field of hydrogels, and therefore, would not be the same as for a skilled person in the field of ocular and topic preparations.

Second, the term "altering the molecular weight" among the mentions of the alteration of a whole range of other parameters does not give any hint to the skilled person about the role of this parameter, the direction of choice for this parameter and the interconnectivity of those parameters in correlation with the resulting effects. At most, *Nettles* is an invitation to start a full research program to study the role of those different parameters in the formation of a porous scaffold for cartilage tissue engineering.

Third, Applicants respectfully submit that the Examiner cannot select one particular aspect or parameter in a prior art reference (in this case the molecular weight) to support some teaching of this reference or some indication of a given motivation to the skilled person out of its context within the rest of the disclosure. In particular, Applicants stress that *Nettles* discloses the use of a 86% deacetylated chitosan having a molecular weight of 200 kDa for the formation of lyophilized microstructures, which, when rehydrated, are put in contact with a tissue culture in order to assess cell viability and attachment to the chitosan scaffold. *Nettles* does not deal with reacetylation of chitosan, nor with hydrogel formation. Therefore, *Nettles* does not teach or suggest a chitosan that would form a pseudo-thermosetting neutralized chitosan

composition forming a phosphate-free transparent hydrogel at a temperature higher than 5°C according to claims 10 and 22.

As such, Applicants respectfully submit that the Examiner's arguments that claims 10 and 22 are rendered obvious by the combination of *Domard* and *Nettles* is not supported.

he Examiner acknowledges that "*use limitations within product claims do not carry patentable weight unless the recitation of the intended use of the claimed invention results in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim*".

Applicants respectfully submit that the use limitations of claims 10 and 22 do result in structural differences between the claimed invention and the prior art. As presented in comparative examples 3, 4, 8, 9, 10 and 11 in the application as originally filed and on Figure 1, the limitations of claims 10 and 22 and the essential features in the formation of a homogeneously reacetylated chitosan suitable for use in the preparation of a pseudo-thermosetting neutralized chitosan composition forming a phosphate free hydrogel of the invention are fully supported.

For the reasons detailed above, Applicants submit that the reacetylated chitosan taught by *Domard* would not intrinsically have the

property of the claimed product under claims 10 and 22, and therefore, the product of claims 10 and 22 is patentably distinct from all of the aforementioned cited art.

In view of the above, Applicants respectfully submit that neither Domard, Industrial Research Catalog, Granja, Varum, Baumann, Nettles or the combination thereof renders claims 10 and 22 obvious. In addition, as discussed above, the chitosans taught by the cited art would not intrinsically have the properties of the claimed product as recited in claims 10 and 22, and therefore, the product of claims 10 and 22 is patentably distinct from the cited art either alone or in combination with any of the cited art.

The Applicants, therefore, respectfully request that the rejection to Claims 8-10 and 22 under 35 U.S.C. § 103(a) be withdrawn.

CONCLUSION

In view of the above remarks and amendments, the Applicants respectfully submit that each of the pending objections and rejections has been addressed and overcome, placing the present application in condition for allowance. A notice to that effect is respectfully requested. If the Examiner believes that personal communication will expedite prosecution of this application, the Examiner is invited to contact the undersigned.

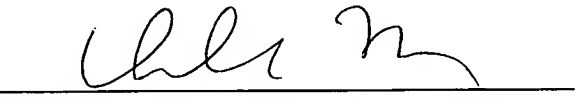
Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Erin G. Hoffman, Reg. No. 57,752, at the telephone number of the undersigned below.

Pursuant to 37 C.F.R. §§ 1.17 and 1.136(a), Applicants hereby petition for a three (3) month extension of time for filing a reply to the outstanding Office Action and submit the required $620.00 extension fee herewith ($490.00 was previously paid).

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 08-0750 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

HARNESS, DICKEY, & PIERCE, P.L.C.

By 

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